REMARKS

Reconsideration of this application is respectfully requested.

Claims 1-51 are presently pending in this application and are presented for further examination. No claims have been amended, added or cancelled by this response.

The Rejection Under 35 U.S.C. §102(b)/103

Claims 1 - 2, 4, 8, 12-14, 19 and 42 - 50 stand rejected under 35 U.S.C. §102(b) as being anticipated by Miller et al. (Biochimie 67:769-776, 1985) for the reasons already of record on page 2 of the Office Action mailed June 5, 1992 (Paper No. 12). In the instant Office Action (page 2), the Examiner stated:

> The applicant argues against this rejection on the basis that Miller et al. only discloses oligonucleotides fully modified with methylphosphonates compared to the partially modified oligomers of the claims. Applicant's arguments filed December 11, 1992 (Paper No. 16) have been fully considered, but they are not deemed persuasive.
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> Applicant does disclose partially modified oligonucleotides that are both resistant to nuclease degradation and yet confer RNAse H sensitive to complementary RNA. **However**, the claims are specifically limited to the characteristic of RNAse sensitivity of the double-stranded DNA/RNA molecule. The instant claims are, in fact, so broad as to read on the completely modified oligomers disclosed by Miller et al.

This ground of rejection is respectfully traversed.

Applicants appreciate the Examiner's comments and particularly, his suggestion for amending the claims in connection with this rejection and the cited Miller et al. disclosure. In response, however, Applicants maintain that the instant invention is novel over Miller et al. As noted in their January 20, 1993 Amendment Under 37 C.F.R. §1.115, the present invention is drawn to a modified nucleotide compound and to methods of identification and treatment. As disclosed in the instant specification (see page 4) and as stated in their January 20, 1993 Amendment (pages 2 and 3), the invention permits the rational design of stable

therapeutically-effective oligo- and polynucleotides. More particularly, until the invention at hand, no one had examined the ability of mixed oligodeoxynucleotides to form RNase H-sensitive substrates as a factor in optimizing antisense function. Moreover, not until the invention at hand had anyone in the art correlated the ability to form RNase H sensitive substrate with nuclease resistance. Thus, there are inter alia at least two major features to the present invention: insensitivity to exo- and endonucleases, and the ability to form RNase H-sensitive hybrids. The latter feature plays an in vivo role in the destruction of messenger RNA. If the antisense oligo is merely a roadblock to ribosomes, it binds to the RNA and blocks ribosome passage. Because RNase H is present in the cells, the antisense oligo can convert the RNA hybrid into a target for RNase H, thereby facilitating the destruction of the RNA rather than merely forming a roadblock to ribosome passage.

As stated in previous responses including Applicants' January 20, 1993 Amendment, Miller et al. discloses fully modified oligonucleotides. Having fully modified their oligonucleotide hybridized to RNA, Miller et al. proposes that the passage of ribosomes can be blocked. Applicants reiterate that RNA itself has loops and double-stranded regions through which ribosomes have no difficulty passing through because the RNA is translated. It is unlikely, therefore, that a small strand of oligonucleotides, such as disclosed by Miller et al., sufficiently blocks ribosomal passage given the fact that RNA is itself double-stranded in various regions. Reading takes place through such double-stranded areas, and the DNA-RNA hybrid that is formed is not as stable as the RNA-RNA hybrid formed by itself. Miller et al. does not even consider that degradation of the RNA can be undertaken in their disclosure. They fully modify the oligonucleotides for protection from nucleases.

Applicants point out that all that is required for sufficient nuclease stability in a nucleotide compound is to modify the ends. In contrast to Miller et al., Applicants unexpectedly discovered that if one modifies at the ends and also has sufficient spacing of the modifications, one can achieve the nuclease stability reported by Miller et al. plus reap the unexpected benefits of forming an RNase H-sensitive hybrid, as discussed above. Thus, the instantly claimed modified nucleotide compounds do not act as mere roadblocks to ribosome passage, as disclosed in Miller et al.; instead, the instant modifications serve a "catalytic-type" function, enhancing sensitivity to RNase H when hybridized to RNA.

As set forth in Applicants' January 20, 1993 Amendment (page 3, last paragraph), an additional feature is achieved by the instant invention over Miller et al. The modified nucleotide compound can cycle from one molecule or polymer of RNA to another because the RNA is destroyed by RNase H. Further, the RNA may be destroyed even before it leaves the nucleus of the cell. Miller et al. does not disclose or even suggest that the RNA can be destroyed because of enhanced RNase H sensitivity; they merely disclose that the passage of ribosomes can be blocked by fully modifying oligodeoxyribonucleosides with methylphosphonate internucleotide bonds.

In view of the foregoing remarks (as set forth in their January 20, 1993 Amendment), Applicants respectfully request reconsideration and withdrawal of the rejection under §102(b).

The Rejection Under 35 U.S.C. §102(b)

Claims 1-4, 12-14 and 42 - 50 stand rejected under 35 U.S.C. §102(b) as being anticipated by Stein et al. (Nucl. Acids. Res. 16(8):3209-3221 (1988)) for the reasons already of record on pages 2-3 of the Office Action mailed June 5, 1992 (Paper No. 12). In the instant Office Action (page 3), the Examiner stated:

> The applicant argues against rejection on the basis that Stein et al. only discloses that the phosphorothioate oligomers only hybridize with RNA homopolymers instead of RNA with all four natural bases. In addition, the applicant notes that the oligomers taught by Stein et al. are fully modified.
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> Applicant's arguments filed December 11, 1992 (Paper No. 16) have been fully considered but are deemed persuasive. Stein et al. shows that the phosphorothioate oligomers from RNA duplexes that are even more sensitive to RNAse H than are duplexes of only phosphodiester linkages. Secondly, the claims are not limited to partially modified oligomers even though the specifications describes such partially modified oligomers.

The anticipation rejection based on Stein et al. is respectfully traversed.

Again, the Examiner's comments and suggestions for amending the claims are appreciated. Applicants respectfully maintain, however, that Stein et al. do not anticipate the instant invention. As noted in Applicants' last response, Stein et al. report on the synthesis, melting

temperatures and nuclease susceptibilities of a series of phosphorothioate oligodeoxynucleotide (ODN) analogs. In contrast to the present invention, Stein et al. do not disclose or suggest that an RNA molecule or polymer with A, C, G and/or U, will be sensitive when hybridized to a known sequence of phosphorothioate oligodeoxynucleotides. They merely show hybridization to form duplexes of poly-rA/s-dT oligomers. Furthermore, the inhibition of HIV activity by phosphorothioate-modified oligodeoxyribonucleotides may not be due to an antisense mechanism at all. Instead, the anti-HIV activity reported by Stein et al. may be just as likely due to inhibition of reverse transcriptase, and other effects, as opposed to the antisense function embraced by the instant invention. Thus, by using Stein's phosphorothioate oligodeoxyribonucleotides for an antisense purpose, one may actually be effecting other deleterious effects on cellular function, including DNA and RNA polymerases. Moreover, Stein's phosphorothioate oligodeoxyribonucleotides are all fully modified, in contrast to the instant "mixed" modified nucleotide compounds. As noted previously, Stein et al. only report or work with a synthetic RNA, which is far different from natural RNA.

In light of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the anticipation rejection.

The Rejection Under 35 U.S.C. §103

Claims 1-51 stand rejected under 35 U.S.C. §103 as being unpatentable over Walder et al. (PNAS 85: 5011, 1988) in view of Inoue et al. (Nucl. Acids Symposium Series 18: 958-976 (1988)) for the reasons already of record on pages 3-5 of the Office Action mailed June 5, 1992 (Paper No. 12). In the instant Office Action (pages 3-4), the Examiner stated:

> The applicant argues against this rejection on the basis that the Walder et al. discloses only methylphosphonate oligomers that do not form RNAse H sensitive duplexes with RNA but only sterically inhibit translation in a cell free systems instead of an intact cell. The applicant also argues that Inoue et al. only discloses partially 2-O-modified oligomers as a probe of RNA structure and not as an antisense inhibitor.
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> Applicant's arguments presented in the paper filed December 11, 1992 (Paper No. 16) have been fully considered but are not deemed persuasive. First, applicant's claims are

not, in fact, limited to partially oligomers but do read on all modified oligomers that are nuclease resistant. Secondly, Inoue et al. clearly teach that a partially modified oligomer with a few as three contiguous phosphodiester bond will form RNAse sensitive duplexes with RNA. The fact that applicant is using both of these criteria in a screening assay in no way makes their broad claims unique and unobvious.

The obviousness rejection is respectfully traversed.

Applicants note that the instant obviousness rejection is based upon a combination of Walder et al. in view of Inoue et al., whereas the obviousness rejection in the June 5, 1992 Office Action was based upon the combination of Walder et al. in view of Miller et al. and Inoue et al.

In response to the rejection, Applicants respectfully maintain that all of Walder's disclosure is directed to an *in vitro* system - having nothing to do with cells. In effect, Walder et al. disclose that there can be RNase H activity in the absence of any modification of the oligonucleotides. Walder et al. show that RNA can be broken up into smaller pieces *in vitro*. Walder et al. perform *in vitro* protein synthesis, demonstrating that if RNase H is present and if an oligodeoxyribonucleotide is hybridized to RNA, the RNA becomes cleaved and protein synthesis is inhibited. Significantly, Walder et al. are working with components in a tube without cells or DNase, and the antisense oligodeoxynucleotides are completely unmodified. With such oligodeoxynucleotides, the only effective way to inhibit translation is to degrade the RNA with an RNase H. Thus, Walder et al. propose a protein-synthesizing system that includes RNase H and has no effect unless an unmodified oligodeoxynucleotides is present as well, that makes the RNA into an RNase H substrate. Hence, no protein synthesis is carried out. Thus Walder's disclosure is not concerned with a ribosome roadblock. Instead, Walder et al. disclose fully unmodified oligodeoxynucleotides which act as a portion of a substrate to inhibit protein synthesis.

With respect to the secondary document, Inoue et al. essentially show that one can probe RNA with a structure that is a partially modified RNA sequence and partially a deoxynucleotide sequence; namely, an oligoribodeoxynucleotide. Inoue's ribonucleotides are modified because RNA is so sensitive to RNase. Therefore, there are 2'-O-methyl groups on the RNA portion of their sequence, then a DNA stretch followed by another modified RNA stretch. In essence, for their disclosed oligonucleotides, Inoue et al. disclose RNA at the end which is modified and resistant to

RNase H because of the modification on the 2' hydroxyl group which inhibits the RNase H. Inoue et al. do not disclose or suggest that such modifications or the modified oligonucleotide splints containing such modifications are resistant to DNase. In fact, Inoue et al. do not even take antisense function or activity into account, i.e., that the RNA has been cleaved to inhibit protein synthesis. Inoue et al. are employing their oligonucleotide splints as a molecular probe to study structure - to cleave specifically a particular RNA molecule. Inoue et al. form a double strand that is recognized specifically and only by RNase H, much in the same way that a restriction enzyme recognizes and cuts specific nucleotide sequences. There is absolutely no contemplation by Inoue et al. to employ their modified oligonucleotide splints as antisense oligos for inhibiting protein synthesis.

In view of the foregoing remarks, Applicants respectfully submit that the combined disclosures of Walder et al. and Inoue et al. are insufficient to have rendered the instant invention obvious to a person of ordinary skill in the art at the time it was made. Reconsideration and withdrawal of the obviousness rejection is, therefore, respectfully requested.

The Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 1 -51 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the instant Office Action (pages 4-5), the Examiner stated:

> Applicant argues against this rejection by incorporating by reference remarks on pages 15-21 of their Amendment B filed February 26, 1992 (Paper No. 11).
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> Applicant's arguments on pages 15-21 of Amendment B filed February 26, 1992 (Paper No. 11) have been fully considered but are not deemed persuasive for the reasons already of record on pages 5-6 of the Office action mailed June 5, 1992 (Paper No. 12).

The indefiniteness rejection is respectfully traversed.

Applicants appreciate that the Examiner fully considered their arguments presented in their February 26, 1992 Amendment. Without

wishing to belabor the issue unduly, however, Applicants are compelled at this point in the prosecution to maintain their position with respect to the definiteness of the instant claims, and to respectfully request reconsideration in view of arguments presented in their February 26, 1992 Amendment.

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SUMMARY AND CONCLUSIONS

Claims 1-51 are presented for further examination. No claims have been amended, added or cancelled by this response.

This Amendment is accompanied by and includes a Request For a Three-Month Extension of Time and authorization for the requisite fee of $420.00 therefor, based upon the instant Assignee's status as a small entity. No other fee is believed due in connection with this response. In the event that any other fee is due, however, The Patent and Trademark Office is hereby authorized to charge Deposit Account No. 05-1135 for the requisite amount of any other such fee for a small entity, as set forth in 37 C.F.R. §1.17(c).

In view of the above discussion of the issues, Applicants respectfully submit that each of claims 1-51 is in condition for allowance. A favorable and speedy reconsideration of their rejection is requested. If any of these claims are found not to be in condition for allowance for any reason, the Examiner is respectfully requested to telephone the undersigned at (212) 856-0876 to discuss the subject application.

Respectfully submitted,

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Date

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